Impact of cigarette smoking on latent tuberculosis infection: does age matter?

To the Editor:

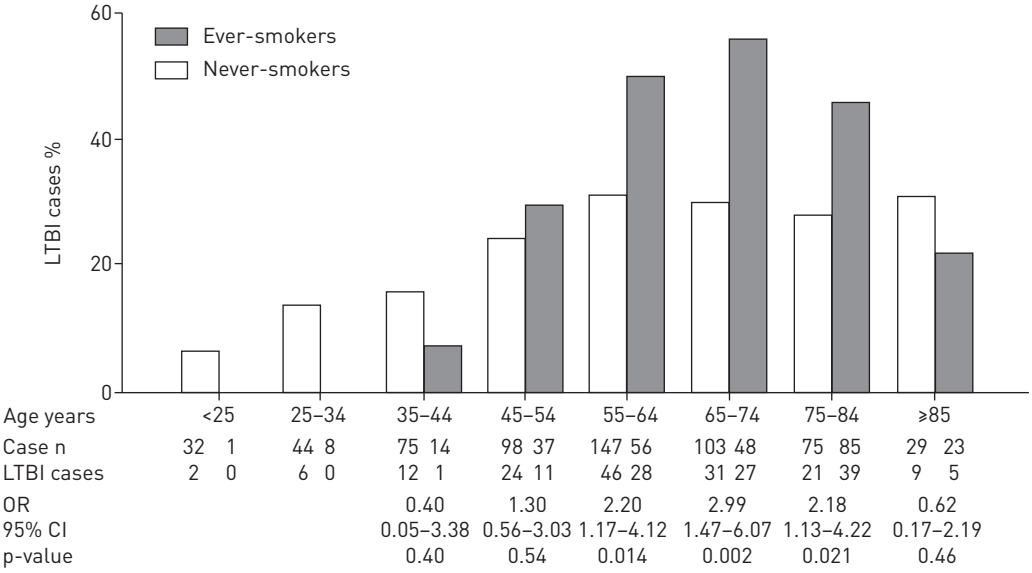
Latent tuberculosis infection (LTBI) is defined by evidence of immunological responses by *Mycobacterium tuberculosis* proteins in the absence of clinical symptoms/signs of active diseases [1]. People who have increased likelihood of tuberculosis (TB) exposure and those with clinical conditions that increased their risk of progressing from LTBI to TB disease are regarded as high-risk groups for developing TB disease and should be considered for LTBI testing and treatment. Both tuberculin skin test (TST) and T-cell based interferon-γ release assays (IGRAs) are available diagnostic tool for LTBI, but IGRAs avoid the interferences from bacille Calmette–Guérin (BCG) vaccination and non-tuberculous mycobacterium (NTM). Cigarette smoke has adverse effects in respiratory immune function and is widely reported to be associated with an increased risk of respiratory a tract infection, including TB [2, 3]. However, only a few studies investigated the impact of smoking on LTBI, and none of these studies used IGRAs to diagnose LTBI [4, 5].

The *European Respiratory Journal* recently published a perspective review focused on the role of diagnosis and treatment of LTBI to improve TB control and eventually TB elimination [6]. To eliminate TB on a global scale the identification and sterilisation of latently infected individuals, especially those in high-risk groups, is of paramount importance. Concerning the close correlation between cigarette smoking and active TB, the association between LTBI and smoking deserves further clarification with IGRAs as a diagnostic tool.

To elucidate the issue, we enrolled inpatients and outpatients who were considered at risk for LTBI and progression to active TB disease from January, 2011 to March, 2012 in a tertiary medical centre in Taiwan. The high-risk individuals enrolled in the present study included people with active TB contact, healthcare workers, and patients with: malignancy, diabetes mellitus, end-stage renal disease, liver cirrhosis, post-organ transplantation, autoimmune diseases, and fibrocalcified lesions suggestive of prior TB on a chest radiograph. Enrolled patients who were under anti-TB treatment or diagnosed with active TB within 1 month of enrolment were excluded. The status of cigarette smoking was collected at the enrolment interview and enrolled patients were divided into ex-smokers, current smokers and never-smokers. The presence of LTBI in enrolled patients was determined by the results of IGRA. The IGRA was performed with QuantiFERON-TB Gold In-Tube (QFT-GIT; Qiagen, Hilden, Germany). The test results were determined as negative, indeterminate, or positive (cut-off at 0.35 $IU \cdot mL^{-1}$) according to the manufacturer's software. Univariate and multivariate analysis were performed to determine the clinical factors associated with LTBI. Statistical analyses were carried out using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA).

During the study period, a total of 955 high-risk individuals were enrolled, 80 of which had indeterminate QFT-GIT results. Ultimately, 875 patients with determinate QFT-GIT results, including 147 (16.8%) former smokers, 125 (14.3%) current smokers, and 603 (68.9%) never-smokers, were included for analysis. The proportions of LTBI cases in ex-smokers, current smokers and never-smokers were 58 (39.5%) out of 147, 53 (42.4%) out of 125, and 151 (25%) out of 603, respectively, which was significantly lower in the never-smokers ($p<0.001$). As compared with never-smokers, ex-smokers and current smokers were older ($p<0.001$), more likely to be male ($p<0.001$), have chronic obstructive pulmonary disease ($p<0.001$), have some malignancy ($p<0.001$), and have fibrocalcified lesions on chest radiographs ($p<0.001$). Ex-smokers and current smokers were less likely to: have a TB-contact history ($p=0.004$), have received a BCG vaccination ($p<0.001$), have certain autoimmune disorders ($p<0.001$), and to be healthcare workers ($p<0.001$) when compared with never-smokers. In multivariate analysis, both ex-smoking (OR 1.64, 95% CI 1.00–2.68) and current smoking (OR 1.88, 95% CI 1.16–3.03) were independent factors associated with LTBI. Other significant factors included increased age (for ex-smoking OR 1.01, 95% CI 1.00–1.03; for current smoking OR 1.02, 95% CI 1.01–1.03) and COPD (for current smoking OR 3.15, 95% CI 1.03–9.69).

We further analysed the impact of smoking in patients with different ages. The proportions of LTBI among various age groups are shown in figure 1. In ever-smokers, the proportions of LTBI dramatically escalated as age increased but declined gradually after the age of 75 years. In never-smokers, the proportions of LTBI also escalated with increasing age but were similar in patients >45 years. The odds ratio of smoking for LTBI in each age group is also shown in figure 1. We found that the odds ratio was higher in elderly patients than those with a younger age, and the highest risk of smoking for LTBI was noted in patients aged from



Age years	<25	25–34	35–44	45–54	55–64	65–74	75–84	≥85
Case n	32 1	44 8	75 14	98 37	147 56	103 48	75 85	29 23
LTBI cases	2 0	6 0	12 1	24 11	46 28	31 27	21 39	9 5
OR			0.40	1.30	2.20	2.99	2.18	0.62
95% CI			0.05–3.38	0.56–3.03	1.17–4.12	1.47–6.07	1.13–4.22	0.17–2.19
p-value			0.40	0.54	0.014	0.002	0.021	0.46

FIGURE 1 Proportions of latent tuberculosis infection (LTBI) among high-risk individuals, stratified by age group and smoking status. Case numbers of overall population and LTBI are presented, and odds ratio of smoking in each age group is analysed using univariate analysis.

65–74 years (OR 2.99, 95% CI 1.47–6.07). Interestingly, the odds ratio rapidly declined in the population aged >85 years.

The occurrences of active TB were documented in eight (1.33%) out of 603 never-smokers and seven (2.57%) out of 272 ever-smokers during the 1-year follow-up period, with the log rank p-value of 0.19 using Kaplan–Meier analysis. 12 of them were documented with LTBI when at enrolment.

Despite extensive studies investigating the association between smoking and active TB, reports evaluating the impact of smoking on LTBI are relatively scarce [4, 5]. To our knowledge, this is the first study that used IGRA to analyse the association between smoking and LTBI. We clearly identified smoking as an independent risk factor for LTBI, both in ex-smokers and current smokers. As compared with previous studies undertaken in TB-endemic areas with TST, our results should be more specific without the potential interferences from BCG vaccination and NTM, especially in TB endemic areas where the BCG vaccination was widely adopted.

The immunological effects of cigarette smoke had been reported in previous studies. Smoke-exposed mice had fewer cytokine-producing macrophages with diminished influx of interferon-γ producing effector T-cells in the lung than mice without smoke exposure [7]. These adverse effects of cigarette smoke in pulmonary immunity contribute to increased incidence of active TB and LTBI. Some clinical studies speculated that the impaired immunity associated with smoking may lower the positive rates of IGRA in active TB cases and HIV patients with LTBI [8, 9]. The controversial findings between the present study and previous reports deserve further clarification in different study populations.

We also found the impact of smoking on LTBI varied with age. Patients with an increased age were more vulnerable to the negative impact of smoking in the occurrence of LTBI. The aged population probably had longer duration and/or higher intensity in cigarette smoking. The immune-suppressive effects of cigarette smoke are probably more prominent in an aged population. The lung structure impairment related to increased intensity of cigarette exposure in aged patients may also increase their susceptibilities to *M. tuberculosis* TB. Therefore, the different impact of intensity and duration of smoking on LTBI deserves further clarification.

The World Health Organization published a monograph to announce the integration of tobacco control into TB programmes in 2007 [10]. However, the importance of smoking in LTBI screening and treatment is so far underestimated. Our findings enhance the evidences that cigarette smoking was an important risk factor associated with a higher prevalence of LTBI. Current and former smokers should be considered as a high-risk population for LTBI and potential candidates for LTBI prophylaxis treatment. Meanwhile, smoking cessation is definitely an important measure to decrease the prevalence of LTBI both in low- and

high-TB prevalence areas. To eliminate TB in the future, the importance of anti-smoking campaigns should not be overlooked.

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Current and ex-smoking is associated with increased risk of LTBI in high-risk individuals, especially in aged populations http://ow.ly/q5FTK

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Received: June 11 2013 | Accepted after revision: Sept 02 2013 | First published online: Sept 26 2013

Support statement: This study was funded by the Institute for Biotechnology and Medicine Industry, Taiwan, R.O.C., and Taipei Veterans General Hospital (V100A-002, V101B-027 and V102B-030).

Conflict of interest: None declared.

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Eur Respir J 2014; 43: 630–632 | DOI: 10.1183/09031936.00118313 | Copyright ©ERS 2014

A tale of two settings: the role of the Beijing genotype in the epidemiology of multidrug-resistant tuberculosis

To the Editor:

Described as a ''template for success'' by HANEKOM *et al.* [1] the Beijing genotype of *Mycobacterium tuberculosis* has been associated with hypervirulence, drug resistance, evasion of the bacille Calmette–Guérin (BCG) vaccine and differential immunoregulation [1]. The genotype is itself diverse; accordingly the fact that specific traits have been associated with Beijing only in certain settings may be explained by the variation in the subtypes that predominate in each.